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TITLE OF THE INVENTION (280 characters max)

PYRIDYL DERIVATIVES
AND THEIR USE AS MGLU5 ANTAGONISTS

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Respectfully submitted,
SIGNATURE _____ Date 03 / 22 / 04

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REGISTRATION NO. (*if appropriate*) 45,263

- [ ] Additional inventors are being named on separately numbered sheets attached hereto

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PYRIDYL DERIVATIVES AND THEIR USE AS MGLU5 ANTAGONISTS

The present invention is directed toward pyridyl derivatives as antagonists of the mGlu5 receptor. As such the compounds may be useful for treatment or prevention of disorders remedied by modulation of the mGlu5 receptor.

BACKGROUND OF THE INVENTION

In the mammalian central nervous system (CNS), the transmission of nerve impulses is controlled by the interaction between a neurotransmitter that is released by an afferent neuron and a surface receptor on a receiving neuron which causes excitation of the receiving neuron. L-Glutamate, which is the most abundant neurotransmitter in the CNS, mediates the major excitatory pathway in mammals and is referred to as an excitatory amino acid (EAA). The receptors that respond to glutamate are called excitatory amino acid receptors. The excitatory amino acids are of great physiological importance playing roles in a variety of physiological processes such as synaptic plasticity, motor control, respiration, cardiovascular regulation and sensory perception. Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed ionotropic. This type of receptor has been subdivided into at least three subtypes which are defined by the depolarizing actions of the selective agonists N-methyl-D-aspartic acid (NMDA), α - amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainic acid (KA). The second general type of receptor is the G-protein or second messenger-linked metabotropic excitatory amino acid receptor.

The metabotropic glutamate (mGlu) receptors belong to the super-family of G-protein coupled receptors and have been divided into three groups based on protein sequence homologies (ref). Molecular cloning and functional expression studies in heterologous cell lines have shown that group I mGlu receptors: mGlu1 and mGlu5 and their spliced isoforms stimulate activation of phospholipase C and mobilization of intracellular calcium whereas the group II (mGlu2 and 3) and III (mGlu4, 6,7 and 8) mGlu receptors negatively modulate adenyl cyclase. Stimulation of mGlu5 (and mGlu1)

receptors promotes an increase in neuronal excitation and fast synaptic transmission via potentiation of NMDA and AMPA receptor mediated responses, induction of depolarization by inhibition of several K^+ channels, activation of Ca_2+-dependent and Ca^{2+} independent non-selective cationic inward currents, enhancement of presynaptic glutamate release and enhancement of Na^+/Ca^{2+} exchange. In addition to the activation of PLC, the signaling of group I mGlu receptors has also been shown to involve activation of other intracellular enzymes including phospholipase D, adenylate cyclase, tyrosine kinase and MAP kinases. In situ studies have shown that mGlu5 splice variants (mGlu5a ,b,c and d) are localized peri- or extra-synaptically on the post synaptic membrane and are expressed in key neuroanatomical sites of the brain and spinal cord associated with psychiatric and neurological dysfunctions.

EP 0 436 398 B1 discloses acetylenes disubstituted with a heteroaromatic group and a substituted phenyl group having retinoid like activity.

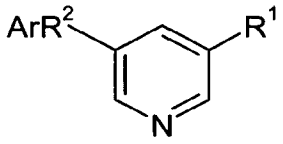
WO 01/16121 discloses heterocyclic compounds and methods of use thereof.

U.S. Patent Publication No. 2003/0225070 A1 discloses phenylethynyl and styryl derivatives of imidazole and fused ring heterocycles.

The compounds of the present invention have now been found to act as antagonists of mGlu5 receptors.

SUMMARY OF THE INVENTION

The present invention comprises a compound of formula I:



(I)

wherein

Ar is aryl or substituted aryl;

R^1 is hydrogen, halo, alkyl, CN, CR^3=NOH, CR^3=NO-alkyl, $(CH)_2$COO-alkyl, OR^3, or CR^3O or CF_3;

R^2 is 1,2-ethenediyl or 1',2-ethynediyl;

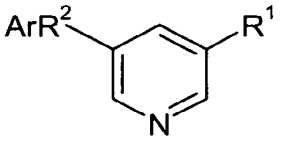
R^3 is hydrogen or alkyl;

or an N-oxide thereof;

or a pharmaceutically acceptable salt thereof;

provided that a compound of formula I does not include one wherein ArR^2 is phenyl-alkynyl and R^1 is CN.

The present invention also provides a method for treating or preventing a disorder remedied by antagonism of mGlu5 in a patient which comprises administering to the patient in need of treatment thereof a pharmaceutically-effective amount of a compound of formula 1:



(I)

wherein Ar is aryl or substituted aryl;

R^1 is hydrogen, halo, alkyl, CN, CR^3=NOH, CR^3=NO-alkyl, $(CH)_2COO$-alkyl, OR^3, or CR^3O or CF_3;

R^2 is 1,2-ethenediyl or 1,2-ethynediyl;

R^3 is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof; or an N-oxide thereof.

In a particular embodiment is R^2 is 1,2-ethynediyl.

In a particular embodiment Ar is phenyl or substituted phenyl. In a more particular referred embodiment Ar is substituted phenyl. In an even more particular embodiment, Ar is 2-, 3- or 4- chlorophenyl , 2-, 3- or 4-fluorophenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,4-dimethylphenyl, 3,6-dimethylphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-, 3- or 4- methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl or 4-methoxyphenyl.

In another particular embodiment for method of treatment, ArR^2 is phenyl-ethynyl and R^1 is CN.

In a particular embodiment R^1 is CN or halo. In a more particular embodiment, R^1 is bromo, iodo, chloro or CN. In an even more particular embodiment, R^1 is CN.

When R^1 or R^3 is alkyl, a particular alkyl group is methyl.

When R^1 is COR^3, a particular value for R^3 is hydrogen.

Preferred compounds of the present invention include: 5-Phenylethynylpyridine-3-carbaldehyde, 3-Methoxy-5-phenylethynylpyridine, or 5-(2,4-Dimethylphenylethynyl)nicotinonitrile.

More preferred compounds of the instant invention include: 5-(2-Methoxyphenylethynyl)nicotinonitrile, 5-Styrylnicotinonitrile, 5-(3,4-Dimethylphenylethynyl)nicotinonitrile, 1-Oxy-5-phenylethynylnicotinonitrile, or 3-Phenylethynylpyridine.

Even more preferred compounds of the instant invention include: 3-Methyl-5-phenylethynylpyridine, 3-Methyl-5-phenylethynylpyridine hydrochloride, 5-Phenylethynylpyridine-3-carbaldehydeoxime, 5-Phenylethynylpyridine-3-carbaldehyde O-methyloxime, 3-(5-Phenylethynylpyridin-3-yl)acrylic acid methyl ester, 3-Bromo-5-phenylethynylpyridine, 5-(2-Chlorophenylethynyl)nicotinonitrile, 5-(3-Chlorophenylethynyl)nicotinonitrile, 5-(2-Fluorophenylethynyl)nicotinonitrile, 5-(3-Fluorophenylethynyl)nicotinonitrile, 5-(4-Fluorophenylethynyl)nicotinonitrile, 5-(3,5-Dimethylphenylethynyl)nicotinonitrile, 5-(3-Cyanophenylethynyl)nicotinonitrile, 5-(2,5-Dimethylphenylethynyl)nicotinonitrile , 5-(3-Methoxyphenylethynyl)nicotinonitrile, 5-(4-Methoxyphenylethynyl)nicotinonitrile, 3-Pyridin-3-ylethynylbenzonitrile hydrochloride, 3-Iodo-5-phenylethynylpyridine, or 3-Chloro-5-phenylethynylpyridine.

Accordingly, the present invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy. In particular, the present invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use as an antagonist of mGlu5 receptors.

In another embodiment, the present invention provides a method for antagonizing mGlu5 receptors, comprising administering to a mammal in need of such inhibition an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. In particular, the present invention provides a method for treating a disorder which is caused by or linked to antagonism of the mGlu5 receptor comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. Such disorders include, for example, psychosis, stroke, pain or Alzheimer's disease.

In another alternative embodiment, the present invention provides for the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for antagonizing mGlu5 receptors. In particular, the present invention provides for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a disorder which is caused by or linked to antagonism of mGlu5 receptors. Such disorders include, for example, psychosis, stroke, pain or Alzheimer's disease.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a tabulation of 37 representative compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the term "effective amount" refers to the amount or dose of the compound, upon single or multiple dose administration to the patient, which provides the desired effect in the patient under diagnosis or treatment.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose of compound administered, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances. For example, a typical daily dose may contain from about 25 mg to about 300 mg of the compound of Formula I. The compounds can be administered by a variety of routes

including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, bucal or intranasal routes. Alternatively, the compound may be administered by continuous infusion.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Particular alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 10 carbon atoms in the chain. Particular alkyl groups have 1 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 3 carbon atoms in the chain which may be straight or branched. When R^1 is CH=NO-alkyl or $(CH)_2COO$-alkyl, the alkyl group is particularly methyl. Where R^1 is COR^3 and R^3 is alkyl, R^3 is particularly lower alkyl.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain in which may be straight or branched. Exemplary alkynyl groups include ethynyl, propynyl or *n*-butynyl.

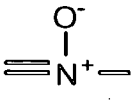
"Aryl" means an aromatic monocyclic or multicycylic ring system of about 6 to 14 carbon atoms, preferably of about 6 to 10 carbon atoms. "Substituted aryl" is substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Representative aryl groups include phenyl or naphthyl. Representative substituted aryl groups include substituted phenyl or substituted naphthyl.

"Halo" is bromo, chloro, iodo or fluoro.

In a specific embodiment, the term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% of a given value or range.

"Ring system substituents" means substituents attached to aromatic or non-aromatic ring systems inclusive of hydrogen, alkyl, alkoxy, acyl, halo, amino, nitro, cyano, hydroxy, acylamino, alkylsulfonylamino or mono-, di- or trifluorinated lower alkyl.

"Alkoxy" means an alkyl-O- group wherein the alkyl group is as herein described. Representative alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy and heptoxy.

"N-oxide" means a moiety of the following structure  .

"Acyl" means an H-CO- or alkyl-CO- group wherein the alkyl group is as herein described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Acylamino" is an acyl-NH- group wherein acyl is as defined above herein.

"Alkylsulfonylamino" means alkyl-SO_2-NH- where the alkyl group is as herein described.

Representative mono, di or trifluoro substituted lower alkyl groups include $-CF_3$,-C_2F_7 or $-C_3F_9$.

The present invention includes pharmaceutically acceptable salts of the compounds of Formula I. "Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulphamates, malonates, salicylates, propionates,

methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methane-sulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinateslaurylsulphonate salts, and the like. (See, for example S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66: p.1-19 (1977) which is incorporated herein by reference.) Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum salts. The sodium and potassium salts are preferred. Suitable inorganic base addition salts are prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide. Suitable amine base addition salts are prepared from amines which have sufficient basicity to form a stable salt, and preferably include those amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use. ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e.g., lysine and arginine, and dicyclohexylamine, and the like.

It will be appreciated that certain compounds of Formula I may possess one or more chiral centers. Where a structural formula does not specify the stereochemistry at one or more chiral centers, it encompasses all possible stereoisomers and all possible mixtures of stereoisomers (including, but not limited to, racemic mixtures) which may result from stereoisomerism at each of the one or more chiral centers.

As mentioned above, the compounds of the present invention and their pharmaceutically acceptable salts antagonize mGlu5 receptors. In view of these properties, the compounds of the present invention and their pharmaceutically acceptable salts may be useful for treating disorders which are remedied by antagonism of mGlu5 receptors. The present invention provides compounds which antagonize mGlu5 receptors and may be useful in the treatment or prevention of mood affective disorders such as anxiety and depression as well as psychosis including bipolar disorder and schizophrenia. In addition compounds of the instant invention may also be useful for the treatment of acute and chronic pain states associated with inflammation, cancer surgery and migraine.

Further, the compounds of the invention may be used in the treatment of acute neurodegenerative diseases, for example stroke, cerebral ischaemia, head and spinal cord trauma, eye injury and chronic neurodegenerative diseases such as, for example, Alzheimer's disease, Parkinson's disease, Amyotropic lateral sclerosis, AIDS-induced dementia, senile dementia, anoxic injuries, and Huntington's Chorea and retinopathy. As antagonists of mGlu5 receptors compounds of the instant invention may be useful for treatment of addictive and compulsive behaviors, substance abuse and drug withdrawal, epilepsy, movement disorders, obesity, emesis, cognitive disorders, circadian rhythm and sleep disorders. Also as mGlu5 antagonists, compounds of the instant invention may be useful for treatment of gastro, esophageal reflux disease as well as for the treatment of regurgitation and asthma.

Accordingly, the present invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy. In particular, the present invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof for use as an antagonist of mGlu5 receptors.

In another embodiment, the present invention provides a method for antagonism of mGlu5 receptors, comprising administering to a patient in need of such inhibition an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. In particular, the present invention provides a method for treating a disorder which is caused by or linked to modulation of the mGlu5 receptor comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. Such disorders include, for example, psychosis, stroke, pain or Alzheimer's disease.

In the context of the present specification the terms "treating" and "treatment" include prophylactic treatment as well as curative treatment.

"Patient" includes both human and other mammals.

In another alternative embodiment, the present invention provides for the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for modulation mGlu5 receptors. In particular, the present invention provides for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disorder which is caused by or linked to modulation of mGlu5 receptors. Such disorders include, for example, psychosis, stroke, pain or Alzheimer's disease.

The compounds may be administered by various routes and are usually employed in the form of a pharmaceutical composition.

Accordingly, in a further embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

Such pharmaceutical compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent or carrier. "Pharmaceutical composition" further refers to a composition comprising a compound of formula I and at least one component selected from the group comprising pharmaceutically acceptale carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Examples of suspending agents include ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of the substances. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monosterate and gelatin. Examples of suitable carriers, diluents, solvents or vehicles include water, ethanol, polyols, suitable mixures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Examples of excipients include lactose, mile sugar, sodium citrate or calcium carbonate. Examples of disintegrating agents include starch, alginic acids and certain complex silicates.
Examples of lubricants include magnesium stearate, sodium lauryl sulphate, talc, as well as high molecular weight polyethylene glycols.

The compositions indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colorants, flavorings and/or one or more further active compounds. Compositions of the invention may be formulated so as to provide,

quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg of the active ingredient.

In the context of the present specification, the term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of one or more compounds of Formula I or pharmaceutically acceptable salts thereof, calculated to produce the desired therapeutic effect, together with a pharmaceutically acceptable diluent or carrier.

Compounds of formula I may be prepared by conventional organic chemistry techniques and also by solid phase synthesis.

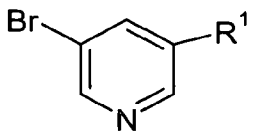
Preparation of Compounds of the Invention

The starting materials and intermediates of compounds of the invention may be prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R. C. Larock in comprehensive Organic Transformations, VCH publishers, 1989.

The invention also provides for a process of preparing a compound of formula I (or a pharmaceutically acceptable salt thereof) which comprises:

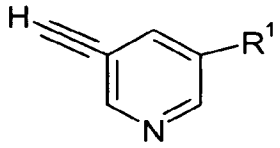
(a) for a compound of formula I in which R^2 is alkenyl, reacting a compound of formula II



(II)

with styrene in a Heck coupling in a suitable solvent, such as DMF, and a suitably substituted aryl group;

(b) for a compound of formula I in which R^2 is alkynyl, reacting a compound of formula III



(III)

in a Sonogashira coupling with a suitably substituted aryl group;

whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of formula I is required, it is obtained by reacting the basic form of such a compound of formula I with an acid affording a physiologically acceptable counterion, or, for a compound of formula I which bears an acidic moiety, reacting the acidic form of such a compound of formula I with a base which affords a pharmaceutically acceptable cation, or by any other conventional procedure; and wherein, unless more specifically described, the values of halo and R^1 are as defined above.

The skilled artisan will appreciate that certain compounds of Formula I may contain at least one chiral center. The present invention contemplates all individual enantiomers, diastereomers or geometric (E/Z) isomers, as well as mixtures of the enantiomers, diastereomers and geometric (E/Z) isomers of said compounds including racemates. The single enantiomers, diastereomers or geometric (E/Z) isomers may be prepared beginning with chiral reagents or by stereoselective or stereospecific synthetic techniques. Alternatively, the single enantiomers, diastereomers or geometric (E/Z) isomers may be isolated from mixtures by standard chiral chromatographic or crystallization techniques.

The compounds of the present invention can be prepared by a variety of procedures, some of which are illustrated in the Schemes below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to provide the compounds of Formula I. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties.

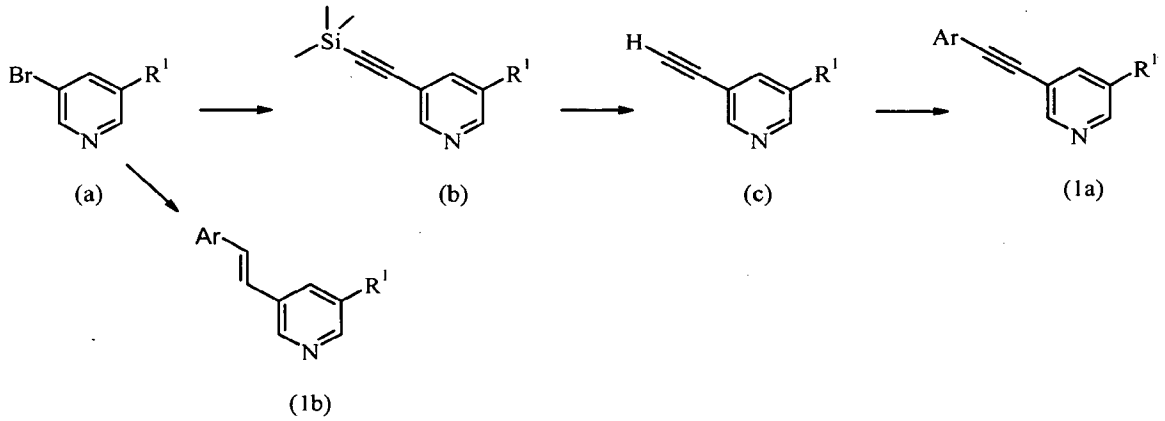
Some substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way.

It will be appreciated that compounds of the present invention may contain asymmetric centers. These asymmetric centers may independently be in either the R or the S configuration. It will be apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula (I) hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallisation techniques, or they are separately prepared from the appropriate isomers of their intermediates.

The compounds of the invention, their methods or preparation and their biological activity will appear more clearly from the examination of the following examples which are presented as an illustration only and are not to be considered as limiting the invention in its scope.

The alkynyl or alkenyl nicotinonitrile analogs may be prepared as illustrated in Scheme 1 where Ar and R^1 are as previously defined.

Scheme 1

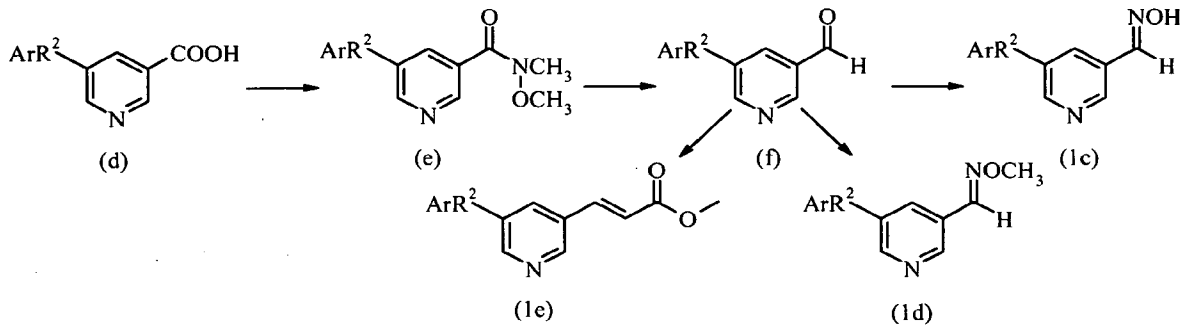


3-R^1-5-bromonicotinotrile (a) is reacted with trimethylsilylacetylene in a palladium catalyzed Sonogashira reaction in triethylamine in a sealed tube to give the silyl protected alkyne (b) after standard extractive and chromatographic techniques. The silyl protecting group is cleaved using standard conditions, such as with

tetrabutylammonium fluoride, to give the alkyne (c) which is then reacted similarly in a Sonogashira coupling with an aryl or substituted aryl group, such as 1-fluoro-4 iodobenzene, to provide 5-aryl-ethynylniconitrile (1a) after standard extractive and chromatographic techniques. Also 3-R^1-5-bromonicotinotrile (a) when treated with styrene in a Heck coupling in a suitable solvent, such as DMF, gives 5-(3-aryl-allyl)nicotinonitrile (1b) after standard extractive and chromatographic techniques.

The hydroxime, methoxime and ester pyridine derivatives may be prepared as illustrated in Scheme 2 where ArR^2 of Formula 1 is as previously defined.

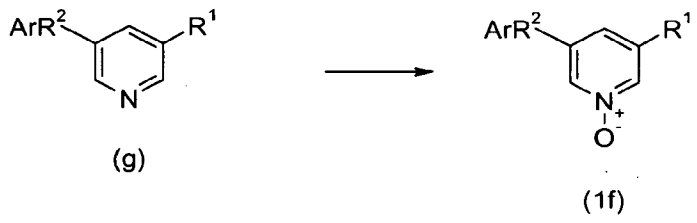
Scheme 2



The substituted nicotinic acid (d) is reacted with N,O-dimethylhydroxylamine hydrochloride with a coupling reagent, such as 1-{3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), in tetrahydron furan in the presence of diisopropylethylamine to give the Weinreb amide (e) after standard extractive and chromatographic techniques. The Weinreb amide is reduced in a suitable solvent, such as toluene, at −78 °C with diisobutylaluminum hydride to give the pyridinecarboxaldehyde (f) after standard extractive and chromatographic techniques. This aldehyde is reacted with hydroxylamine hydrochloride or methoxylamine hydrochloride in a suitable solvent, such as ethanol, with a base like potassium carbonate to give the resultant compounds (1c) and (1d) after standard extractive and chromatographic techniques. Also pyridinecarboxaldehyde (f) is reacted with methyl(triphenylphosphoranylide)acetate in a suitable solvent, such as dichloromethane, to give compound (1e) as the pyridineacrylic acid methyl ester after standard extractive and chromatographic techniques.

The pyridine-N-oxide analogs may be prepared as illustrated in Scheme 3 where ArR^2, and R^1 of Formula 1 are as previously defined.

Scheme 3



The substituted pyridine analog (g) is dissolved in a suitable solvent, such as dichloromethane, and oxidized using perrhenic acid to give the pyridine-N-oxide compound (1f) after standard extractive and chromatographic techniques.

The following examples are provided to further describe the invention and are not to be construed as limitations thereof.

EXAMPLES

PREPARATION 1

3-Bromo-5-methylpyridine

Add cesium carbonate (1.38 g, 4.22 mmol), trimethylboroxine (0.2 mL, 1.47 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.488 g, 0.42 mmol) to a solution 3,5-dibromonicotinonitrile (1.0 g, 4.22 mmol) in 9:1 dioxane:water (10 mL) and stir under nitrogen at 110 °C for 16 h. Add more trimethylboroxine (0.2 mL, 1.47 mmol) and stir at 100 °C for an additional 16 h. Cool the reaction mixture to ambient temperature, filter through Celite®, and wash with ethyl acetate. Concentrate the filtrate and purify the residue by silica gel chromatography, eluting with 80:20 hexanes:ethyl acetate, to give the title compound as a colorless oil (0.654 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 7.66 (s, 1 H), 8.36 (s, 1 H), 8.49 (s, 1 H).

GC-MS (EI): *m/z* = 171.0, 173.0 [M].

PREPARATION 2

N-Methoxy-N-methyl-5-phenylethynylnicotinamide

Add EDCI (3.86g, 20.2mmol) and diisopropylethylamine (7.0 mL, 40.3 mmol) to a suspension of 5-phenylethynylnicotinic acid (3.0 g, 13.4 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.97 g, 20.2 mmol) in THF (100mL) and stir at ambient temperature overnight. Concentrate the reaction mixture, dissolve the residue in ethyl acetate and wash sequentially with an aqueous solution of Phosphate buffer (pH = 7) and a saturated aqueous solution of sodium chloride. Dry the organic layer over magnesium sulfate, filter and concentrate. Purify the residue by silica gel chromatography, eluting with 50:50 ethyl acetate:hexanes, to give the title compound as a pale yellow solid (2.4g, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.58 (s, 3H), 7.39-7.37 (m, 3H), 7.56-7.54 (m, 2H), 8.15 (d, J = 2.4 Hz, 1H), 8.81 (d, J = 2.0 Hz, 1H), 8.87 (d, J = 1.6 Hz, 1H).

MS (ES): $m/z = 267$ $[M+H]^+$.

PREPARATION 3

5-Trimethylsilanylethynylnicotinonitrile

Combine 5-bromonicotinonitrile (10.0 g, 53.0 mmol), bis(triphenylphosphine)palladium (II) chloride (1.86 g, 2.65 mmol), copper (I) iodide (1.04 g, 5.46 mmol) and triethylamine (50 mL, 359 mmol) in a sealed tube under nitrogen and treat with (trimethylsilyl)acetylene (8.00 mL, 56.75 mmol). Stir the resultant black reaction mixture at 70 °C for 1.7 h and cool to ambient temperature. Dilute the reaction mixture with ethyl acetate, wash with a saturated aqueous solution of sodium chloride and dry over sodium sulfate. Filter and concentrate *in vacuo*. Dissolve the residue in dichloromethane and filter through a pad of Celite®/silica gel. Wash with 80:20 dichloromethane:ethyl acetate. Concentrate the filtrate to give 11.6 g of the title compound as a tan solid. See PREPARATION 4. The crude material is purified by silica gel chromatography eluting with 95:5 to 85:15 hexanes:ethyl acetate to afford analytically pure 5-trimethylsilanyl-ethynyl-nicotinonitrile.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.31 (m, 9H), 8.03 (t, J = 2.3 Hz, 1H), 8.81 (d, J = 2.0 Hz, 1H), 8.87 (d, J = 2.3 Hz, 1H). MS (ES) m/z 201.2 $[M+H]^+$. HRMS Calcd for $C_{11}H_{13}N_2Si$ 201.0848. Found 201.0857. Anal Calcd for $C_{11}H_{12}N_2Si$: C, 65.96; H, 6.04; N, 13.98. Found: C, 65.72; H, 6.12; N, 13.91.

PREPARATION 4

5-Ethynylnicotinonitrile

Dissolve 5-trimethylsilanylethynylnicotinonitrile (11.45 g, 57.16 mmol), prepared as described in PREPARATION 3, in tetrahydrofuran (400 mL) and treat with a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (62.9 mL, 62.9 mmol). After 5 min, dilute the reaction mixture with ethyl acetate (800 mL) and wash sequentially with water and a saturated aqueous solution of sodium chloride. Dry the organic layer over sodium sulfate, filter, and concentrate. Purify the residue by silica gel chromatography, eluting with a gradient of 100:0 to 90:10 dichloromethane:ethyl acetate to give the title compound as a yellow crystalline solid (3.46 g, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 1H), 8.07 (s, 1H), 8.95 (br m, 2H).

PREPARATION 5

3-Trimethylsilanylethynylbenzonitrile

Add trimethylsilylacetylene (3.4 mL, 24.0 mmol) to a mixture of bis(triphenylphosphine)palladium (II) chloride (766mg, 1.1 mmol), copper (I) iodide (416mg, 2.2 mmol) and 3-iodobenzonitrile (5 g, 21.8 mmol) in triethylamine (20 mL). Upon addition of the trimethylsilylacetylene an exothermic reaction occurs and after about 4 min the reaction mixture solidifies. Cool the reaction mixture for about 15 min, dilute with ethyl acetate (100 mL), filter through fluted filter paper using ethyl acetate and concentrate. Dissolve the residue in ethyl acetate (200 mL) and wash sequentially with an aqueous solution of 0.1 N hydrochloric acid and a saturated aqueous solution of sodium chloride. Dry the organic layer over sodium sulfate, filter and concentrate. Purify the residue by silica gel chromatography, eluting with 0:100 to 5:95 ethyl acetate:hexanes, to give the title compound as a tan solid (3.6 g, 83%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.29 (s, 9H), 7.45 (t, J = 8.0 Hz, 1H), 7.60-7.63 (m, 1H), 7.68-7.71 (m, 1H), 7.77-7.78 (m, 1H). LC-MS (ES): *m/z* = 200.0 $[M+H]^+$.

PREPARATION 6

Trifluoromethanesulfonic acid 5-fluoropyridin-3-yl ester

Add triethylamine (0.65 mL, 4.64 mmol) and N-phenyltrifluoromethanesulfonimide (1.58 g, 4.43 mmol) to a solution of 5-fluoro-pyridin-3-ol (0.5 g, 4.42 mmol) in dichloromethane (11 mL) at 0 °C and stir under nitrogen for 1 h. Warm the reaction mixture to room temperature and stir overnight. Wash the reaction mixture sequentially with an aqueous solution of 1 M sodium hydroxide and water. Dry over sodium sulfate and concentrate the organic layer to obtain the title compound as a volatile oil (0.568 g, 52%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.47 (dt, J = 8.0 Hz, 2.4 Hz, 1 H), 8.47 (s, 1 H), 8.57 (t, J = 2.0 Hz, 1 H). GC-MS (EI): *m/z* = 245.0 [M].

PREPARATION 7

3-Chloro-5-trifluoromethylpyridine

Add zinc dust (1.18 g) to a suspension of 2,3-dichloro-5-trifluoromethyl-pyridine (2.0 g, 9.30 mmol) in 80:20 water and acetic acid (5 mL) and stir at 90 °C for 1 h. Add more zinc dust (1 g) and stir at 90 °C for an additional 15 min. Cool the reaction mixture to room temperature, filter, and wash with dichloromethane. Carefully concentrate and purify the residue by silica gel chromatography, eluting with 100:0 to 0:100 hexanes:dichloromethane, to obtain the title compound as a volatile oil (0.120g, 7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 8.78 (s, 2 H). GC-MS (EI): *m/z* = 181.0, 183.0 [M].

EXAMPLE 1

3-Methyl-5-phenylethynylpyridine

Add phenylacetylene (0.460 mL, 4.2 mmol), copper (I) iodide (0.072 g, 0.38 mmol) and bis(triphenylphosphine)palladium (II) dichloride (0.133 g, 0.19 mmol) to a solution of 3-bromo-5-methylpyridine (10.654 g, 3.8 mmol), prepared as described in PREPARATION 1, in degassed triethylamine (20 mL) and stir under nitrogen at 80 °C for 16 h. Cool the reaction mixture to ambient temperature, filter through Celite®, wash with ethyl acetate, and concentrate. Purify the residue by silica gel chromatography, eluting with 80:20 hexanes:ethyl acetate, to give the title compound as a brown oil (0.398 g, 54%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 7.39-7.35 (m, 3 H), 7.56-7.52 (m, 2 H), 7.65 (s, 1 H), 8.39 (s, 1 H), 8.58 (s, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.6, 86.4, 92.8, 120.3, 123.9, 128.8, 129.1, 132.1, 133.1, 139.4, 149.4, 149.6. MS (ES): *m/z* = 194.1 $[M+H]^+$.

EXAMPLE 2

3-Methyl-5-phenylethynylpyridine hydrochloride

Add a 4 N solution of hydrogen chloride in 1,4-dioxane (0.6 mL) to a solution of 3-methyl-5-phenylethynylpyridine (0.398 g, 2.06 mmol), prepared as described in

EXAMPLE 1, in diethyl ether (2 mL). Concentrate the reaction mixture and triturate the resulting solid with hexanes and diethyl ether to give the title compound as a solid (0.477 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 3 H), 7.43-7.41 (m, 3 H), 7.57-7.55 (m, 2 H), 8.26 (br s, 1 H), 8.62 (br s, 1 H), 8.69 (br s, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 19.5, 82.1, 98.5, 120.9, 124.6, 129.1, 130.7, 132.6, 138.6, 140.3, 140.9, 147.9. MS (ES): *m/z* = 194.1 $[M+H]^+$.

EXAMPLE 3

3-Phenylethynylpyridine

Add phenylacetylene (0.175 mL, 1.6 mmol), copper (I) iodide (0.028 g, 0.15 mmol) and bis(triphenylphosphine)palladium (II) dichloride (0.051 g, 0.07 mmol) to a solution of 3-bromopyridine (0.140 mL, 1.45 mmol) in degassed triethylamine (6 mL) and stir under nitrogen at 80 °C for 16 h. Cool the reaction mixture to ambient temperature, filter through Celite®, wash with ethyl acetate, and concentrate. Purify the residue by silica gel chromatography, eluting with 100:0 to 0:100 hexanes:dichlormethane to give the title compound (91.1 mg, 35%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (br s, 1 H), 7.33-7.39 (m, 3 H), 7.52-7.57 (m, 2 H), 7.84 (d, J = 1.6 Hz, 1 H), 8.61 (br s, 1 H), 8.83 (br s, 1 H).

MS (ES): *m/z* = 180 $[M+H]^+$.

EXAMPLE 4

1-Oxy-5-phenylethynylnicotinonitrile

Add bis(trimethylsilyl)peroxide (3 ml, 15 mmol) to a suspension of 5-phenylethynylnicotinonitrile (2.04 g, 10 mmol) and 65-70% perrhenic acid (8.5 µl, 0.05 mmol) in dichloromethane (1.5 ml) and stir at room temperature for 24 h. Add dichloromethane (1.5 mL) and stir for an additional 8 h. Dilute the reaction mixture with hexanes (30 mL) and collect the solid. Purify the solid by silica gel chromatography, eluting with 100:0 to 0:100 dichloromethane:ethyl acetate and recrystallize in ethyl acetate to give the title compound as a white solid (910 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (t, J = 1.4 Hz, 1 H), 8.33 (t, J = 1.4 Hz, 1 H), 7.57 (t, J = 1.4 Hz, 1 H), 7.54 (m, 2 H), 7.43 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 140.7, 132.4, 130.6, 130.2, 129.1, 125.1, 121.1, 113.9, 113.2, 97.7, 81.8. MS (ES): *m/z* = 221 $[M+H]^+$.

EXAMPLE 5

5-Phenylethynylpyridine-3-carbaldehyde

Charge an oven dried round bottom flask under nitrogen with a solution of N-methoxy-N-methyl-5-phenylethynylnicotinamide (2.00 g, 7.51 mmol), prepared as described in PREPARATION 2, in anhydrous toluene (20 mL) and cool to –78 °C. Add a 1 M solution of diisobutylaluminum hydride in toluene (18 mL, 18 mmol) dropwise over 30 min and stir for an additional 30 min. Rapidly add methanol (15 mL) and warm to ambient temperature. Pour the reaction mixture into 100 mL of a saturated aqueous solution of Rochelle salt and stir vigorously for about 30 min. Upon standing, separate the organic layer, dry over magnesium sulfate, filter and concentrate. Purify the residue by silica gel chromatography, eluting with 50:50 hexanes:ethyl acetate, to obtain the title compound as a white solid (1.2 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.41 (m, 3H), 7.55-7.58 (m, 2H), 8.26-8.27 (m, 1H), 8.98 (dd, J = 13.6, 2.0 Hz, 2H), 10.13 (s, 1H). LC-MS (ES): *m/z* = 208 $[M+H]^+$.

EXAMPLE 6

5-Phenylethynylpyridine-3-carbaldehydeoxime hydrochloride

Dissolve 5-phenylethynylpyridine-3-carbaldehyde (0.19 g, 0.70 mmol), prepared as described in EXAMPLE 5, in ethanol (2.0 mL) and sequentially add potassium carbonate (0.48 g, 3.5 mmol) and hydroxylamine hydrochloride (0.39 g, 5.6 mmol). Heat the reaction mixture at reflux for 3 h, cool to ambient temperature and filter. Concentrate the filtrate and purify by reverse phase chromatography (ISCO-130™ C18 column), using a linear gradient of 0% to 100% over 40 min. and a mobile phase of water (0.05% trifluoroacetic acid) and acetonitrile to obtain the trifluoroacetic acid salt of the title compound.

Dissolve the above trifluoroacetic acid salt of the title compound in diethyl ether with enough dichloromethane to obtain a homogenous solution and add a 1 N solution of hydrochloric acid (0.5 mL, 1.1 eq to trifluoroacetic acid salt) in diethyl ether. Stir at ambient temperature for 2 h and filter to give the title compound, after drying, as a solid (0.12 g, 65%).

^{1}H NMR (400 MHz, CD_3OD): δ 7.46-7.49 (m, 3H), 7.65 (dd, J = 7.6 Hz, 1.6 Hz, 2H), 8.29 (s, 1H), 8.75 (s, 1H), 8.99 (s, 2H). LC-MS (ES): *m/z* = 223 $[M+H]^+$. Anal Calcd for $C_{14}H_{10}N_2O$- HCl: C, 64.99; H, 4.28; N, 10.82. Found C, 65.17; H, 4.40; N, 10.79.

EXAMPLE 7

5-Phenylethynylpyridine-3-carbaldehyde O-methyloxime hydrochloride

Dissolve 5-phenylethynylpyridine-3-carbaldehyde (0.20 g, 0.97 mmol), prepared as described in EXAMPLE 5, in ethanol (2.0 mL) and sequentially add potassium carbonate (0.67 g, 4.8 mmol) and methoxyamine hydrochloride (0.64 g, 5.6 mmol). Heat at reflux overnight, cool to ambient temperature and filter. Concentrate the filtrate and purify by silica gel chromatography, eluting with a linear gradient of 90:10 to 50:50 hexanes:ethyl acetate to obtain the free base of the title compound as a colorless oil.

Dissolve the above free base of the title compound in diethyl ether and add a 1 N solution of hydrochloric acid in diethyl ether (0.9 mL, 1.1 eq to free base). Stir at ambient temperature for 2 h and filter to give the title compound, after drying under high vacuum overnight, as a solid (0.22g, 84%).

^{1}H NMR (400 MHz, CD_3OD): 4.06 (s, 3H), 7.46 (d, J = 7.2 Hz, 2H), 7.47 (s, 1H), 7.63 (dd, J = 7.6, 1.2 Hz, 2H), 8.30 (s, 1H), 8.76 (s, 1H), 8.97 (d, J = 9.2 Hz, 2H). LC-MS (ES): *m/z* = 237 $[M+H]^+$.

EXAMPLE 8

3-(5-Phenylethynylpyridin-3-yl)acrylic acid methyl ester hydrochloride

Dissolve 5-phenylethynyl-pyridine-3-carbaldehyde (0.20 g, 0.97 mmol), prepared as described in EXAMPLE 5, and methyl(triphenylphosphoranylide)acetate (0.36 g, 1.1 mmol) in dichloromethane (3.0 mL) and stir at ambient temperature overnight. Concentrate the reaction mixture and purify the residue by silica gel chromatography,

eluting with a linear gradient of 90:10 to 50:50 hexanes:ethyl acetate, to obtain the free base of the title compound as a white solid.

Dissolve the above free base of the title compound in diethyl ether and add a 1 N solution of hydrochloric acid in diethyl ether (0.92 mL, 1.1 eq to free base). Stir at ambient temperature for 2 h, filter and dry to give the title compound as a solid (0.25g, 86%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H), 6.97 (d, J = 16.0 Hz, 1H); 7.45-7.47 (m, 3H); 7.63-7.65 (m, 2H); 7.80 (d, J = 16.4 Hz, 1H), 8.93 (s, 1H), 9.02 (s, 1H), 9.06 (s, 1H). LC-MS (ES): *m/z* = 264 $[M+H]^+$.

EXAMPLE 9

3-Bromo-5-phenylethynylpyridine

Add phenylacetylene (1.11 mL, 10.10 mmol) dropwise to a mixture of 3,5-dibromopyridine (2.05 g, 8.65 mmol), bis(triphenylphosphine)palladium (II) chloride (300 mg, 0.427 mmol), and copper (I) iodide (160 mg, 0.840 mmol) in triethylamine (8.50 mL, 60.98 mmol) and stir for 3 h at room temperature. Dilute the reaction mixture with ethyl acetate and wash with a saturated aqueous solution of sodium chloride. Dry the ethyl acetate layer over sodium sulfate, filter and concentrate. Purify the residue by silica gel chromatography using 120 g of silica, eluting with a gradient of 100:0 to 90:10 hexanes:ethyl acetate, to give the title compound (710 mg, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.43 (m, 3H), 7.57-7.59 (m, 2H), 8.00 (t, J = 2.2 Hz, 1H), 8.65 (d, J = 1.8 Hz, 1H), 8.70 (br s, 1H). MS (ES): *m/z* = 258.0 (99%), 260.0 (100%) $[M+H]^+$. HRMS Calcd for $C_{13}H_9BrN$ 257.9918. Found 257.9921.

EXAMPLE 10

5-(2-Chlorophenylethynyl)nicotinonitrile

Add bis(triphenylphosphine)palladium (II) chloride (63.2 mg, 0.090 mmol), copper (I) iodide (34.3 mg, 0.180 mmol), and 5-ethynylnicotinonitrile (242 mg, 1.89 mmol), prepared as described in PREPARATION 4, to a solution of 1-chloro-2-iodobenzene (0.22 mL, 1.77 mmol) in triethylamine (3.60 mL, 25.8 mmol) and heat to 70 °C in a sealed tube for 1.5 h. Cool the reaction mixture to ambient temperature and dilute

with ethyl acetate. Wash with a saturated aqueous solution of sodium chloride, dry over sodium sulfate, filter, and concentrate *in vacuo*. Purify the residue by silica gel chromatography, eluting with a gradient from 95:5 to 80:20 A:B, where A is 90:10 hexanes:ethyl acetate and B is dichloromethane to give the title compound as a yellow solid. Further purify the title compound by recrystallizing from cyclohexane (20 mL) to give a white solid (95 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dt, J = 7.5 Hz, 1.3 Hz, 1H), 7.39 (dt, J = 7.5 Hz, 1.8 Hz, 1H), 7.51 (dd, J = 7.9 Hz, 1.3 Hz, 1H), 7.62 (dd, J = 7.5, 1.8 Hz, 1H), 8.14 (t, J = 2.2 Hz, 1H), 8.86 (br s, 1H), 9.00 (br s, 1H). HRMS Calcd for $C_{14}H_8ClN_2$ 239.0376. Found 239.0384. Anal Calcd for $C_{14}H_7ClN_2$: C, 70.45; H, 2.96; N, 11.74. Found: C, 70.01; H, 3.02; N, 11.23.

EXAMPLE 11

5-(3-Chlorophenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 10 using 1-chloro-3-iodobenzene (0.22 mL, 1.77 mmol) to give the title compound (165 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, J = 7.9 Hz, 1H), 7.42-7.45 (m, 1H), 7.48 (td, J = 7.5 Hz, 1.3 Hz, 1H), 7.59 (t, J = 1.8 Hz, 1H), 8.10 (t, J = 1.8 Hz, 1H), 8.86 (br s, 1H), 8.96 (br s, 1H). HRMS Calcd for $C_{14}H_8ClN_2$ 239.0376. Found 239. 0376. Anal Calcd for $C_{14}H_7ClN_2 \cdot 0.1H_2O$: C, 70.45; H, 2.96; N, 11.74. Found: C, 69.85; H, 2.92; N, 11.36.

EXAMPLE 12

5-(2-Fluorophenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 10 using 1-fluoro-2-iodobenzene (0.22 mL, 1.89 mmol) to give the title compound (50 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.24 (m, 2H), 7.42-7.47 (m, 1H), 7.58 (dt, J = 7.0 Hz, 1.8 Hz, 1H), 8.13 (t, J = 2.2 Hz, 1H), 8.85 (d, J = 1.8 Hz, 1H), 8.98 (d, J = 1.8 Hz, 1H). HRMS Calcd for $C_{14}H_8FN_2$ 223.0671. Found 223.0695. Anal Calcd for $C_{14}H_7FN_2$: C, 75.67; H, 3.18; N, 12.60. Found: C, 75.45; H, 3.32; N, 12.53.

EXAMPLE 13

5-(3-Fluorophenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 10 using 1-fluoro-3-iodobenzene (0.22 mL, 1.87 mmol) to give the title compound (50 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.19 (m, 1H), 7.27-7.30 (m, 1H), 7.36-7.44 (m, 2H), 8.11 (t, J = 1.8 Hz, 1H), 8.86 (br s, 1H), 8.96 (br s, 1H). HRMS Calcd for $C_{14}H_8FN_2$ 223.0671. Found 223.0691. Anal Calcd for $C_{14}H_7FN_2 \cdot 0.1H_2O$: C, 75.06; H, 3.24; N, 12.51. Found: C, 74.85; H, 3.21; N, 12.20.

EXAMPLE 14

5-(4-Fluorophenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 10 using 1-fluoro-4-iodobenzene (0.22 mL, 1.91 mmol) to give the title compound (50 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.16 (m, 2H), 7.56-7.60 (m, 2H), 8.09 (t, J = 2.2 Hz, 1H), 8.83 (d, J = 1.8 Hz, 1H), 8.95 (d, J = 1.8 Hz, 1H). HRMS Calcd for $C_{14}H_8FN_2$ 223.0671. Found 223.0669. Anal Calcd for $C_{14}H_7FN_2$: C, 75.67; H, 3.18; N, 12.60. Found: C, 75.61; H, 3.21; N, 12.51.

EXAMPLE 15

5-Styrylnicotinonitrile

Add tris(dibenzylideneacetone)dipalladium (125 mg, 0.136 mmol) and tri-*o*-tolylphosphine (86 mg, 0.273 mmol) to a solution of triethylamine (0.77 ml, 5.46 mmol), 5-bromonicotinonitrile (500 mg, 2.73 mmol) and styrene (0.48 ml, 4.1 mmol) in 10 ml of anhydrous DMF under an inert atmosphere, and stir at 100 °C for 3.5 h. Cool the reaction mixture to room temperature, add water and extract three times with diethyl ether. Combine the organic layers, dry over sodium sulfate, filter, and concentrate. Purify the residue by silica gel chromatography, eluting with dichloromethane, to give the title compound as a white solid (190 mg, 34%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (d, J = 1.9 Hz, 1H); 8.73 (d, J = 1.9 Hz, 1H); 8.07 (t, J = 1.9 Hz, 1H); 7.56-7.52 (m, 2H); 7.44-7.32 (m, 3H); 7.23 (d, J = 16.0 Hz, 1H); 7.05 (d,

J = 16.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2; 150.3; 135.7; 135.5; 133.7; 133.5; 129.1; 128.9; 126.9; 122.3; 116.5; 110.1; MS (ES): *m/z* = 207 $[M+H]^+$.

EXAMPLE 16

5-(3,4-Dimethylphenylethynyl)nicotinonitrile

Combine 4-iodo-o-xylene (0.362 g, 1.561 mmol), bis(triphenylphosphine)palladium (II) chloride (55 mg, 0.078 mmol), and copper (I) iodide (30 mg, 0.156 mmol) in triethylamine (0.653 mL, 4.683 mmol) and stir under nitrogen for 5 min at 80 °C. Add a solution of 5-ethynylnicotinonitrile (200 mg, 1.561 mmol), prepared as described in PREPARATION 4, in anhydrous acetonitrile (2.50 mL), and stir under nitrogen overnight. Cool the reaction mixture to room temperature and dilute with diethyl ether. Wash with a saturated aqueous solution of sodium bicarbonate, dry over sodium sulfate, filter, and concentrate. Purify the residue by silica gel chromatography, eluting with 95:5 to 50:50 dichloromethane:ethyl acetate, to give the title compound as a yellow solid (225 mg, 62%).

^{1}H NMR (400 MHz, CD_3OD) δ 2.32 (s, 3H), 2.34 (s, 3H), 7.21 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 8.33 (t, J = 2.0 Hz, 1H), 8.87 (br s, 1H), 8.94 (br s, 1H). LC-MS (ES): *m/z* = 233 $[M+H]^+$.

EXAMPLE 17

5-(3,5-Dimethylphenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 16 using 5-iodo-m-xylene (246 mg, 1.061 mmol). Purify by silica gel chromatography, eluting with a gradient of 95:5 to 60:40 dichloromethane:ethyl acetate, to give the title compound as a white solid (60 mg, 24%).

^{1}H NMR (400 MHz, CD_3OD) δ 2.35 (s, 6H), 7.13 (s, 1H), 7.24 (s, 2H), 8.34 (t, J = 2.0 Hz, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.94 (d, J = 2.2 Hz, 1H). LC-MS (ES): *m/z* = 233 $[M+H]^+$.

EXAMPLE 18

5-(2,4-Dimethylphenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 16 using 4-Iodo-m-xylene (362 mg, 1.561 mmol). Purify by silica gel chromatography, eluting with a gradient of 95:5 to 60:40 dichloromethane:ethyl acetate, to give the title compound as a tan solid (247 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.51 (s, 3H), 7.06 (d, J = 7.9 Hz, 1H), 7.12 (s, 1H), 7.44 (d, J = 7.9 Hz, 1H), 8.06-8.08 (m, 1H), 8.84 (br s, 1H), 8.95 (br s, 1H). LC-MS (ES): *m/z* = 233 $[M+H]^+$.

EXAMPLE 19

5-(2,5-Dimethylphenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 16 using 2-iodo-p-xylene (362 mg, 1.561 mmol). Purify by silica gel chromatography, eluting with a gradient of 95:5 to 60:40 dichlromethane:ethyl acetate, to give the title compound as an off-white solid (183 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.50 (s, 3H), 7.13-7.21 (m, 2H), 7.37 (s, 1H), 8.07 (s, 1H), 8.83 (br s, 1H), 8.96 (br s, 1H). LC-MS (ES): *m/z* = 233 $[M+H]^+$.

EXAMPLE 20

5-(2-Cyanophenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 10 using 2-iodobenzonitrile (0.45 g, 2.0 mmol) to give the title compound (35 mg, 4%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dt, J = 1.7, 7.6 Hz, 1H), 7.64-7.80 (m, 3H), 8.18 (t, J = 2.0 Hz, 1H), 8.88 (d, J = 2.0 Hz, 1H), 9.03 (d, J = 2.3 Hz, 1H). HRMS Calcd for $C_{15}H_8N_3$ 230.0718. Found 230.0730. Anal Calcd for $C_{15}H_7N_3$: C, 78.59; H, 3.08; N, 18.33. Found: C, 78.33; H, 3.12; N, 18.09.

EXAMPLE 21

5-(3-Cyanophenylethynyl)nicotinonitrile

Prepare essentially as described in EXAMPLE 10 using 3-iodobenzonitrile (0.45 g, 2.0 mmol) to give the title compound (140 mg, 31%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dt, J = 0.7 Hz, 7.9 Hz, 1H), 7.73 (td, J = 1.3 Hz, 7.9 Hz, 1H), 7.81 (td, J = 1.3 Hz, 7.9 Hz, 1H), 7.87-7.88 (m, 1H), 8.12 (t, J = 2.0 Hz, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 2.0 Hz, 1H). HRMS Calcd for $C_{15}H_8N_3$ 230.0718. Found 230.0739.

EXAMPLE 22

5-(4-Cyanophenylethynyl)nicotinonitrile

Prepare essentially as described in EXAMPLE 10 using 4-iodobenzonitrile (0.45 g, 2.0 mmol) to give the title compound (173 mg, 44%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.67 (m, 4H), 8.13 (s, 1H), 8.87 (s, 1H), 8.97 (s, 1H). HRMS Calcd for $C_{15}H_8N_3$ 230.0718. Found 230.0754. Anal Calcd for $C_{15}H_7N_3$: C, 78.59; H, 3.08; N, 18.33. Found: C, 78.09; H, 3.05; N, 17.97.

EXAMPLE 23

5-(2-Methoxyphenylethynyl)nicotinonitrile

Prepare essentially as described in EXAMPLE 10 using 2-iodoanisole (0.46 g, 2.0 mmol) to give the title compound (40 mg, 9%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.0 (q, J = 7.9 Hz, 1H), 7.40-7.45 (m, 1H), 7.53 (dd, J = 1.3 Hz, 7.6 Hz, 1H), 8.11 (t, J = 2.0 Hz, 1H), 8.81 (t, J = 2.0 Hz, 1H), 8.97 (d, J = 2.0 Hz, 1H). HRMS Calcd for $C_{15}H_{11}N_2O_1$ 235.0871. Found 235.0868.

EXAMPLE 24

5-(3-Methoxyphenylethynyl)nicotinonitrile

Prepare essentially as described in EXAMPLE 10 using 3-iodoanisole (0.46 g, 2.0 mmol) to give the title compound (38 mg, 8%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.01 (ddd, J =1.0 Hz, 2.6 Hz, 8.2 Hz, 1H), 7.10-7.11 (m, 1H), 7.17-7.20 (m, 1H), 7.34 (t, J = 8.2 Hz, 1H), 8.10 (t, J = 2.0 Hz, 1H),

8.83 (d, J = 2.0 Hz, 1H), 8.95 (d, J = 2.0 Hz, 1H). HRMS Calcd for $C_{15}H_{11}N_2O_1$ 235.0871. Found 235.0848.

EXAMPLE 25

5-(4-Methoxyphenylethynyl)nicotinonitrile

Prepare essentially as described in EXAMPLE 10 using 4-iodoanisole (0.46 g, 2.0 mmol) to give the title compound (44 mg, 10%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.93-6.97 (m, 2H), 7.51-7.55 (m, 2H), 8.07 (t, J = 2.0 Hz, 1H), 8.80 (d, J = 2.0 Hz, 1H), 8.92 (d, J = 2.0 Hz, 1H). HRMS Calcd for $C_{15}H_{11}N_2O_1$ 235.0871. Found 235.0890. Anal Calcd for $C_{15}H_{10}N_2O_1$: C, 76.91; H, 4.30; N, 11.96. Found: C, 76.67; H, 4.39; N, 11.83.

EXAMPLE 26

3-Pyridin-3-ylethynylbenzonitrile

Add triethylamine (5 mL) to a stirring mixture of 3-iodopyridine (1.03 g, 5.03 mmol), bis(triphenylphosphine)palladium (II) chloride (176 mg, 0.252 mmol), copper (I) iodide (96 mg, 0.503 mmol), and 3-trimethylsilanylethynylbenzonitrile, prepared as described in PREPARATION 5 (1.0 g, 5.03 mmol), at –78 °C. After about 3 min, add a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (5.03 mL, 5.03 mmol) in one portion, warm to room temperature and stir overnight. Filter the reaction mixture through fluted filter paper and concentrate the filtrate under vacuum. Dissolve the residue in ethyl acetate and wash sequentially with a saturated solution of aqueous sodium bicarbonate and a saturated solution of aqueous sodium chloride. Dry the ethyl acetate layer over sodium sulfate, filter, and concentrate. Purify the residue by silica gel chromatography, using a gradient of 0:100 to 40:60 ethyl acetate:hexanes followed by a second silica gel chromatography using a gradient elution of 0:100 to 40:60 ethyl acetate:dichloromethane to give the title product as a yellow solid (730 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.67-7.70 (m, 1H), 7.78-7.81 (m, 1H), 7.87-7.89 (m, 2H), 8.60-9.10 (br m, 2 H). LC-MS (ES): *m/z* = 205 $[M+H]^+$.

EXAMPLE 27

3-Pyridin-3-ylethynylbenzonitrile hydrochloride

Bubble anhydrous hydrogen chloride gas through a solution of 3-pyridin-3-ylethynyl-benzonitrile prepared as described in EXAMPLE 26 (730 mg, 3.58 mmol) in anhydrous diethyl ether (160 mL) at 0 °C for about 2 min and concentrate. Triturate the solid with diethyl ether, filter, and wash with diethyl ether to give the title compound, after drying under vacuum, as a light tan solid (789 mg, 92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (t, J = 8.4 Hz, 1H), 7.85 (br s, 1H), 7.97 (dd, J = 1.4 Hz, 8.2 Hz, 2H), 8.15-8.16 (m, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.70-9.3 (br m, 2H). LC-MS (ES): *m/z* = 205 $[M+H]^+$.

EXAMPLE 28

3-Iodo-5-phenylethynylpyridine

Heat a mixture of 3-bromo-5-phenylethynylpyridine (5.71 g, 22.12 mmol), prepared as described in EXAMPLE 9, copper (I) iodide (211 mg, 1.1 mmol), sodium iodide (6.63 g, 44.24 mmol) and N,N'-dimethylethylendiamine (0.24 mL, 2.21 mmol,) in 1,4-dioxane (20 mL) at 110 °C for 60 h. Cool to room temperature, dilute with ethyl acetate and wash with a saturated aqueous solution of sodium chloride, and dry the organics over sodium sulfate. Purify the residue by silica gel chromatography, eluting with 15:1 hexanes:ethyl acetate to give the title compound (5.45 g, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.40 (m, 3 H), 7.49-7.56 (m, 2 H), 8.15 (dd, J = 2.0, 1.6 Hz, 1 H), 8.68 (d, J = 1.6 Hz, 1 H), 8.75 (d, J = 2.0 Hz, 1 H). MS (ES): *m/z* = 306 $[M+H]^+$.

EXAMPLE 29

3-Chloro-5-phenylethynylpyridine

Charge a Schlenk tube under a positive pressure of argon with bis(acetonitrile)palladium (II) chloride (5 mg), 2-dicyclohexylphosphino diphenyl (21 mg), cesium carbonate (1.69 g, 5.2 mmol) and 3,5-dichloropyridine (0.3 g, 2 mmol) in acetonitrile and stir at room temperature for 25 min. (Angew. Chem. Int. Ed. 42, 5993-

5996, (2003). Add phenylacetylene (0.285 mL, 2.6 mmol) and stir at 95 °C for 16 h. Dilute the reaction mixture with water and diethyl ether and separate the phases. Wash the organic layer with water, concentrate and purify the residue by silica gel chromatography, eluting with 50:50 hexanes:dichloromethane to obtain the title compound (68 mg, 16%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.39 (m, 3 H), 7.53-7.56 (m, 2 H), 7.80 (t, J = 2.0 Hz, 1 H), 8.50 (d, J = 2.4 Hz, 1 H), 8.62 (d, J = 1.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.9, 94.3, 121.9, 122.4, 128.9, 129.6, 132.0, 132.2, 138.3, 147.9, 150.2. MS (ES): *m/z* = 316.3, 318.4 $[M+H]^+$.

EXAMPLE 30

3-Methoxy-5-phenylethynylpyridine

Add phenylacetylene (0.180 mL, 1.6 mmol), copper (I) iodide (0.029 g, 0.15 mmol) and bis(triphenylphosphine)palladium (II) dichloride (0.053 g, 0.08 mmol) to a solution of 3-bromo-5-methoxypyridine (0.282 g, 1.5 mmol) in degassed triethylamine (8 mL) and heat at 80 °C for 16 h. Cool the reaction mixture to room temperature, filter through Celite®, wash with ethyl acetate, and concentrate. Purify the residue by silica gel chromatography, eluting with 50:50 to 0:100 hexanes:ethyl acetate to give the title compound (0.206 g, 66%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 3 H), 7.44-7.47 (m, 3 H), 7.56-7.60 (m, 3 H), 8.85 (br s, 1 H). MS (ES): *m/z* = 210 $[M+H]^+$.

EXAMPLE 31

3-Hydroxy-5-phenylethynylpyridine

Add boron tribromide (1 mL, 1 mmol) dropwise to solution of 3-methoxy-5-phenylethynylpyridine (0.073 g, 0.35 mmol), prepared as described in EXAMPLE 30, in dichloromethane (0.7 mL) at –78 °C and stir for 15 min. Warm the reaction mixture to room temperature and stir overnight. Add a saturated aqueous solution of sodium bicarbonate to the reaction mixture and stir for 10 min. to provide a biphasic solution. Separate the organic layer and wash it sequentially with a saturated solution of aqueous sodium bicarbonate and a saturated aqueous solution of sodium chloride. Dry the organic

layer with sodium sulfate, concentrate and purify by silica gel chromatography, eluting with 100:0 to 0:100 hexanes:ethyl acetate, to obtain the title compound (0.003 g, 4%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.41-7.47 (m, 4 H), 7.56-7.59 (m, 3 H), 8.13 (s, 1 H), 8.24 (s, 1 H). MS (ES): *m/z* = 196.2 $[M+H]^+$.

EXAMPLE 32

3-Fluoro-5-phenylethynylpyridine

Add phenylacetylene (0.180 mL, 1.6 mmol), copper (I) iodide (0.015 g, 0.08 mmol) bis(triphenylphosphine)palladium (II) dichloride (0.027 g, 0.04 mmol) and triethylamine (0.85 mL, 6 mmol) to a solution of trifluoromethanesulfonic acid 5-fluoro-pyridin-3-yl ester (0.367 g, 1.5 mmol), prepared as described in PREPARATION 6, in degassed ethyl acetate (1.5 mL) and heat at 60 °C for 16 h. Cool the reaction mixture to room temperature, filter through Celite®, wash with ethyl acetate, and concentrate. Purify the residue by silica gel chromatography, eluting with dichloromethane, to give the title compound (0.192 g, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.38 (m, 3 H), 7.48 (s, 1 H), 7.51-7.56 (m, 2 H), 8.44 (br s, 1 H), 8.59 (br s, 1 H). ^{13}C NMR (75MHz, $CDCl_3$) δ 85.0, 94.1, 122.4, 125.2, 125.4, 128.9, 129.5, 132.2, 137.4, 137.7, 148.5. MS (ES): *m/z* = 198.1 $[M+H]^+$.

EXAMPLE 33

3-Trifluoromethyl-5-phenylethynylpyridine

Charge a sealed tube under a positive pressure of argon with bis(acetonitrile)palladium (II) chloride (18 mg, 0.07 mmol), 2-dicyclohexylphosphino diphenyl (73 mg, 0.21 mmol), cesium carbonate (0.557 g, 1.71 mmol) and 3-Chloro-5-trifluoromethylpyridine (0.12 g, 0.66 mmol), prepared as described in PREPARATION 7, in acetonitrile and stir at room temperature for 25 min (Angew. Chem. Int. Ed. 42, 5993-5996, (2003). Add phenylacetylene (0.1 mL, 0.86 mmol) and stir at 100 °C for 16 h. Cool to room temperature, dilute the reaction mixture with water, and wash twice with ethyl acetate. Combine the ethyl acetate layers, dry over sodium sulfate, and concentrate. Purify the residue by silica gel chromatography, eluting with 100:0 to 50:50 hexanes:dichloromethane, to obtain the title compound (30 mg, 10%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.41 (m, 3 H), 7.54-7.59 (m, 2 H), 8.05 (s, 1 H), 8.81 (s, 1 H), 8.93 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.7, 94.9, 121.2, 121.7, 122.2, 125.3, 126.8 (q), 128.9, 129.7, 132.2, 135.7, 145.4, 155.4. GC-MS (EI): *m/z* = 247.1 [M].

EXAMPLE 34

5-(4-Chlorophenylethynyl)nicotinonitrile

Prepare according to the general procedure outlined in EXAMPLE 10 using 1-chloro-3-iodobenzene (0.22 mL, 1.77 mmol) to give the title compound (160 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.43 (m, 2H), 7.51-7.53 (m, 2H), 8.10 (t, J = 1.8 Hz, 1H), 8.85 (br s, 1H), 8.96 (br s, 1H). HRMS Calcd for $C_{14}H_8ClN_2$ 239.0376. Found 239.0378. Anal Calcd for $C_{14}H_7ClN_2 \cdot 0.2H_2O$: C, 69.40; H, 3.08; N, 11.56. Found: C, 69.37; H, 3.10; N, 11.41.

EXAMPLE 35

5-(2-Methylphenylethynyl)nicotinonitrile

Prepare essentially as described in EXAMPLE 10 using 2-iodotoluene (0.51 g, 2.34 mmol) to give the title compound (143.4 mg, 16%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3H), 7.2-7.4 (m, 3H), 7.54 (d, J=7.92 Hz, 1H), 8.09 (t, J=1.98 Hz, 1H), 8.83 (d, J=1.98 Hz, 1H), 8.95 (d, J=1.65 Hz, 1H). MS (ES): *m/z* = 219 $[M+H]^+$.

EXAMPLE 36

5-(3-Methylphenylethynyl)nicotinonitrile

Prepare essentially as described in EXAMPLE 10 using 3-iodotoluene (0.51 g, 2.34 mmol) to give the title compound (191.1 mg, 37%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.2-7.4 (m, 4H), 8.07-8.08 (m, 1H), 8.82 (s, 1H), 8.95 (s, 1H). MS (ES): *m/z* = 219 $[M+H]^+$.

EXAMPLE 37

5-(4-Methylphenylethynyl)nicotinonitrile

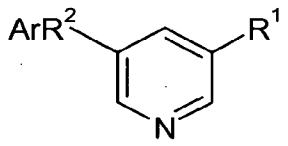
Prepare essentially as described in EXAMPLE 10 using 4-iodotoluene (0.51 g, 2.34 mmol) to give the title compound (32 mg, 6%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.2-7.5 (m, 4H), 8.06-8.07 (m, 1H), 8.81 (s, 1H), 8.94 (s, 1H). MS (ES): *m/z* = 219 $[M+H]^+$.

Compounds of the present invention were evaluated for effects on glutamate induced calcium flux responses using an AV-12 cell line expressing human recombinant mGlu5a receptor protein (see *Kingston et al Neuropharmacology. 37(1):1-12, 1998*). mGlu5 receptor mediated responses were determined by changes in intracellular calcium concentrations measured by a fluorescent calcium sensitive dye Fluo-3. Cells were harvested and seeded into 96 well microtiter plates. After 48h incubation in a humidified incubator at 37°C , the cells were loaded with 10uM fluo-3 AM dye for 60min at 25°C. Unincorporated extracellular dye was removed from the wells by washing with buffer solution and plates were then transferred to a 96-channel fluorimetric imaging plate reader (FLIPR- Molecular Devices Corporation, La Jolla, CA, USA). Baseline fluorescence readings were undertaken for 10 seconds prior to addition of test compounds by an automatic pipetting device integral to the FLIPR instrument. Following a 20 second delay, glutamate was then added to the wells at an EC90% concentration (10uM) and changes in fluorescence monitored over 60 seconds. The inhibitory effects of the compounds were determined by comparing the peak fluorescence response to glutamate in the presence and absence of compound. IC50 values were calculated using a 4 parameter logistic curve fitting program (GraphPad ™ Software). Preferrable compounds of the present invention which were tested according to the assay described above exhibit an IC50 of <10uM. More preferable compounds exhibit on IC5O <1uM. The most preferable compounds exhibit an IC5O or <100nM

We Claim:

1. A method for treating a disorder remedied by antagonism of mGlu5 in a patient which comprises administering to the patient in need of treatment thereof an effective amount of a compound of formula 1:



(I)

wherein Ar is aryl or substituted aryl;

R^1 is hydrogen, halo, alkyl, CN, CR^3=NOH, CR^3=NO-alkyl, $(CH)_2COO$-alkyl, OR^3, or CR^3O or CF_3;

R^2 is 1,2-ethenediyl or 1,2-ethynediyl;

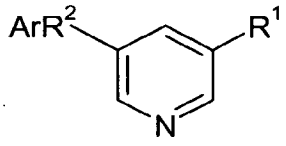
R^3 is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof; or an N-oxide thereof.

2. A method for treating a disorder remedied by antagonism of mGlu5 in a patient which comprises administering to the patient in need of treatment thereof an effective amount of a compound of formula I as claimed in Claim 1 wherein ArR^2 is phenylmethynyl and R^1 is CN.

3. The method of Claim 1 wherein the disorder is pain, impairment of cognition, drug dependency, anxiety, depression or psychosis.

4. The present invention comprises a compound of formula I:



(I)

wherein

Ar is aryl or substituted aryl;

R^1 is hydrogen, halo, alkyl, CN, CR^3=NOH, CR^3=NO-alkyl, $(CH)_2COO$-alkyl, OR^3, or CR^3O or CF_3;

R^2 is 1,2-ethenediyl or 1,2-ethynediyl;

R^3 is hydrogen or alkyl;

or an N-oxide thereof;

or a pharmaceutically acceptable salt thereof;

provided that a compound of formula I does not include one wherein ArR^2 is phenyl-alkynyl and R^1 is CN.

5. A pharmaceutically acceptable salt of a compound of formula I as claimed in Claim 4 which is an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion or, for a compound which contains an acidic moiety, which is a salt made with a base which provides a pharmaceutically acceptable cation.

6. The compound of formula I as claimed in Claims 4 or 5 wherein R^1 is CN, iodo, chloro, methyl or COR^3.

7. The compound of formula I as claimed in Claims 4-6 wherein R^1 is CN.

8. The compound of formula I as claimed in Claims 4-7 wherein R^2 is 1,2-ethynediyl.

9. The compound of formula I as claimed in Claims 4-8 wherein alkyl is methyl.

10. The compound of formula I as claimed in Claims 4-9 wherein R^3 is methyl.

11. A compound of Claims 4-9 wherein R^3 is hydrogen.

12. The compound of formula I as claimed in Claims 4-11 wherein Ar is phenyl or substituted phenyl.

13. The compound of formula I as claimed in Claims 4-12 wherein Ar is substituted phenyl.

14. The compound of formula I as claimed in Claims 4-13 wherein Ar is 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,4-dimethylphenyl, 3,6-dimethylphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-methoxyphenyl, 3-methoxyphenyl or 4-methoxyphenyl.

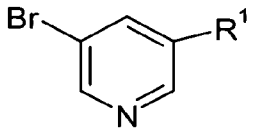
15. A compound of formula 1 as claimed in Claim 4 selected from the group consisting of:

3-Methyl-5-phenylethynylpyridine, 3-Methyl-5-phenylethynylpyridine hydrochloride, 3-Phenylethynylpyridine, 1-Oxy-5-phenylethynylnicotiononitrile, 5-phenylethynylpyridine-3-carbaldehyde, 5-phenylethynylpyridine-3-carbaldehydeoxime hydrochloride, 5-phenylethynylpyridine-3-carbaldehyde O-methyloxime hydrochloride, 3-(5-phenylethynylpyridin-3-yl)acrylic acid methyl ester hydrochloride, 3-bromo-5-phenylethynylpyridine, 5-(2-chlorophenylethynyl)nicotinonitrile, 5-(3-chlorophenylethynyl)nicotinonitrile, 5-(2-fluorophenylethynyl)nicotinonitrile, 5-(3-fluorophenylethynyl)nicotinonitrile, 5-(4-fluorophenylethynyl)nicotinonitrile, 5-styrylinicotinonitrile, 5-(3,4-Dimethylphenylethynyl)nicotinonitrile, 5-(3,5-Dimethylphenylethynyl)nicotinonitrile, 5-(2,4-Dimethylphenylethynyl)nicotinonitrile, 5-(2,5-Dimethylphenylethynyl)nicotinonitrile, 5-(2-Cyanophenylethynyl)nicotinonitrile, 5-(3-Cyanophenylethynyl)nicotinonitrile, 5-(4-Cyanophenylethynyl)nicotinonitrile, 5-(2-Methoxyphenylethynyl)nicotinonitrile, 5-(3-Methoxyphenylethynyl), 5-(4-Methoxyphenylethynyl)nicotinonitrile, 3-Pyridin-3-ylethynylbenzonitrile, 3-Pyridin-3-ylethynylbenzonitrile hydrochloride, 3-Iodo-5-phenylethynylpyridine, 3-Chloro-5-phenylethynylpyridine, 3-Methoxy-5-phenylethynylpyridine, 3-

Hydroxy-5-phenylethynylpyridine, 3-Fluoro-5-phenylethynylpyridine, 3-Trifluoromethyl-5-phenylethynylpyridine, 5-(4-Chlorophenylethynyl)nicotinonitrile, 5-(2-Methylphenylethynyl)nicotinonitrile, 5-(3-Methylphenylethynyl)nicotinonitrile, 5-(4-Methylphenylethynyl)nicotinonitrile.

16. A process for preparing a compound of formula I (or a pharmaceutically acceptable salt thereof) as provided in any one of the above Claims 4-15 which comprises:

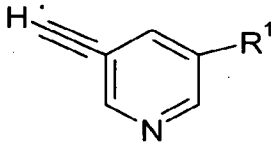
(a) for a compound of formula I in which R^2 is alkenyl, reacting a compound of formula II



(II)

with styrene in a Heck coupling in a suitable solvent, such as DMF, and a suitably substituted aryl group;

(b) for a compound of formula I in which R^2 is alkynyl, reacting a compound of fomula III



(III)

in a Sonogashira coupling with a suitably substituted aryl group;

whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of formula I is required, it is obtained by reacting the basic form of such a compound of formula I with an acid affording a physiologically acceptable

counterion, or, for a compound of formula I which bears an acidic moiety, reacting the acidic form of such a compound of formula I with a base which affords a pharmaceutically acceptable cation, or by any other conventional procedure; and wherein, unless more specifically described, the value of R^1 is as defined in Claim 4.

17. A pharmaceutical formulation comprising in association with a pharmaceutically acceptable carrier, dilutent or excipient, a compound of formula I (or a pharmaceutically acceptable salt thereof) as provided in any one of the above Claims 4-15.

18. A process for preparing the compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in Claim 4.

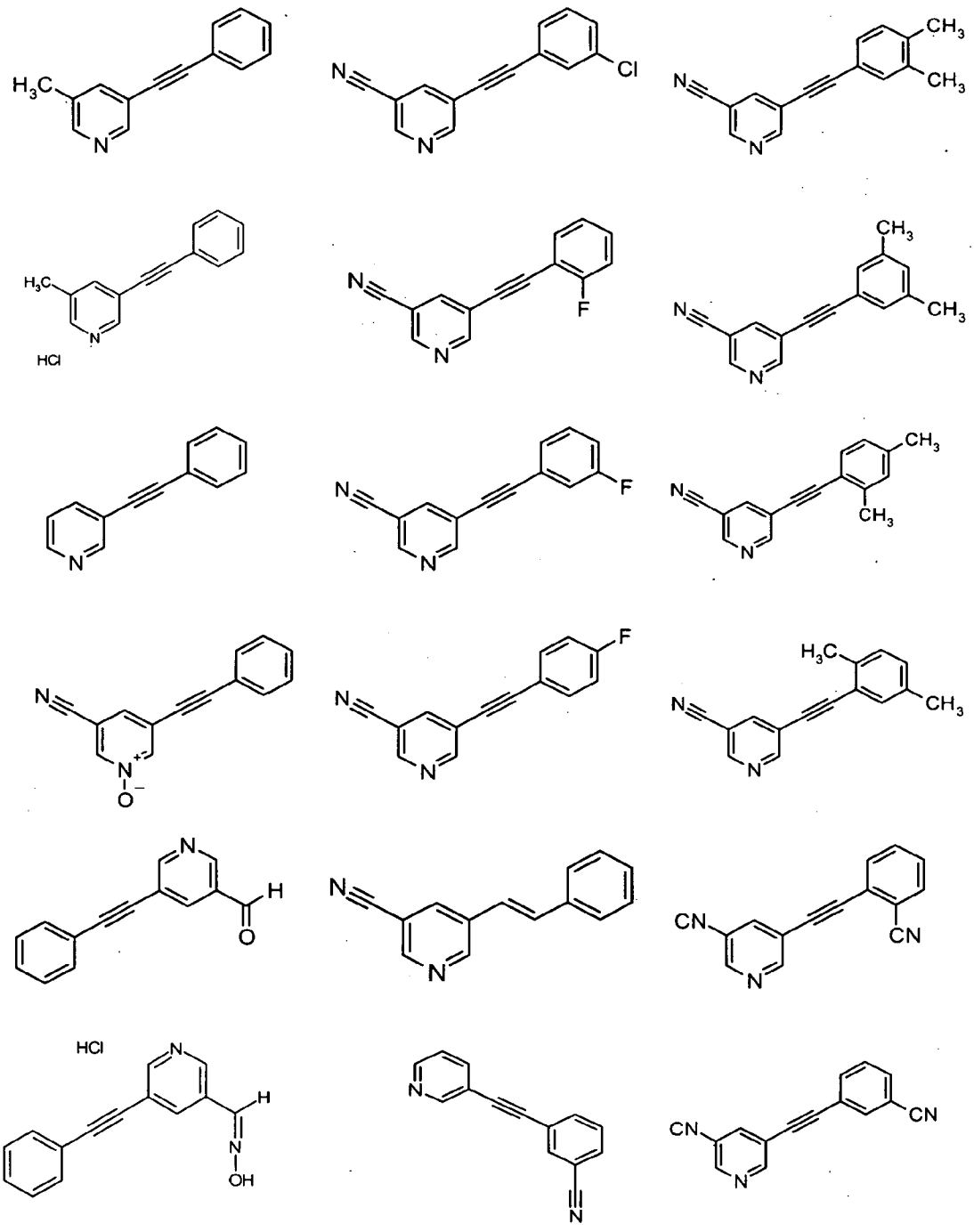
19. A novel compound of formula I substantially as hereinbefore described with reference to any of the Examples.

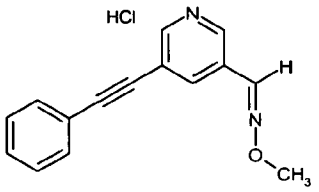
20. A process for preparing a novel compound of formula I substantially as hereinbefore described with reference to any of the Examples.

ABSTRACT

The present invention is directed toward pyridyl derivatives as antagonists of the mGlu5 receptor. As such the compounds may be useful for treatment or prevention of disorders remedied by modulation of the mGlu5 receptor.

Figure 1

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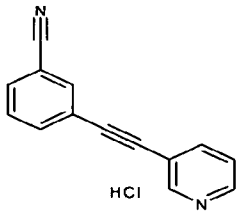
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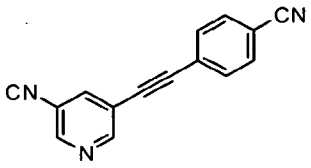
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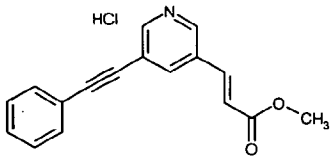
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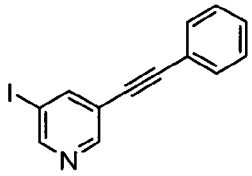
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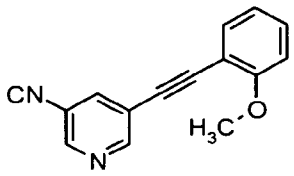
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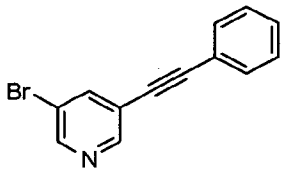
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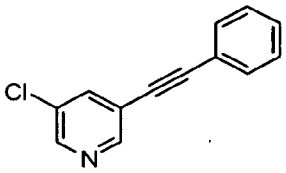
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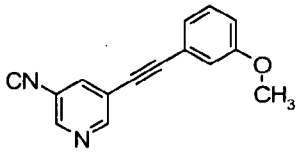
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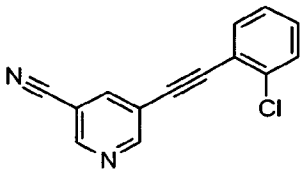
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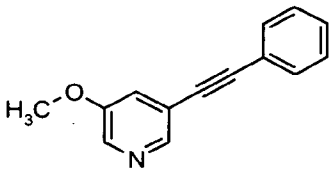
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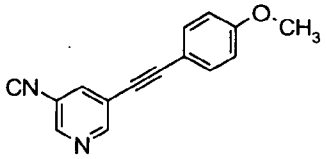
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